Real-World Data of Nivolumab and Pembrolizumab in Platinum Refractory Advanced Non-Small Cell Lung Cancer: Potential Practical Predictors of Treatment

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ABSTRACT

The aim of the study was to investigate the real-world nivolumab and pembrolizumab efficacy in patients with platinum-refractory advanced non-small cell lung cancer (NSCLC). We also sought the role of clinicopathologic prognostic and predictive factors. All consecutive patients aged over 18 years who were diagnosed as having platinum-refractory metastatic NSCLC and received at least one dose of nivolumab or pembrolizumab treatment at Dr. Burhan Nalbantoglu State Hospital (Nicosia, Cyprus) and Near East University Hospital (Nicosia, Cyprus) between March 2017 and October 2021 were retrospectively reviewed from patient files, the center's databases, and chemotherapy ward files. A total of 56 patients treated with nivolumab and pembrolizumab were retrospectively reviewed. The majority of patients (n= 48; 85.7%) received Immune checkpoint inhibitors (ICIs) as second-line therapy and nivolumab was the most commonly (n= 51; 91.1%) used ICI. The median progression-free survival (PFS) and overall survival (OS) were 7.06 (95% CI: 4.43-9.69) months and 11.63 (95% CI: 7.65-15.61) months, respectively. In the entire study population, the objective response rate and disease control rate was 50.0% (complete response: 16.1%, partial response: 33.9%) and 60.7%, respectively. The median duration of responses was 26.40 months (95% CI: 4.17-48.76) (range, 0.67+ to 40.70+ months, with + indicating an ongoing response at the time of analysis). In the multivariate analysis, immun-related adverse events were independently associated with better PFS and OS. This bi-centric real-world data demonstrated that ICIs are standard of care in patients with platinum-refractory advanced NSCLC.

Keywords: Platinum refractory advanced NSCLC, Nivolumab, Pembrolizumab, Real-world, anti-PD1 Antibodies

INTRODUCTION

Evasion from the immune system is a hallmark feature of cancer development and progression.[1] The discovery of immune system harnessing using anti-programmed death-1 (PD-1) or anti-programmed death ligand-1 (PD L-1) blockade has led to a renaissance in cancer treatment. Immune checkpoint inhibitors (ICIs) have caused a paradigm shift in the last decade in the treatment landscape of advanced non-small cell lung cancer (NSCLC) whose tumors do not harbor genomic alterations.

In several clinical trials, ICIs treatment significantly improved overall survival (OS) compared with chemotherapy. Consequently, ICIs became the standard of care, initially for patients who progressed with platinum-based chemotherapy and then either alone or combined with chemotherapy for the first-line treatment of advanced NSCLC.[2-8] Much of the experience with ICIs are from randomized controlled trials (RCTs), where stringent inclusion criteria were used, but in everyday clinical practice, the majority of the patients are unsuitable for clinical trials.[9,10]

As a result, there are concerns that the therapeutic benefits observed in clinical trials are not fully reflected in the real world.

Although ICIs treatment has become the standard of treatment in patients with platinum-refractory advanced NSCLC, a considerable number of patients are still unresponsive, progressing, and dying of cancer.[2-5] Furthermore, ICIs cause serious financial toxicitiy. Hence, determining predictive biomarkers for ICIs treatment is an important subject. The PD-L1 level has become a companion diagnostic assay for first-line treatment in patients with advanced NSCLC whose tumors do not harbor genomic alterations.[6-8] In patients with platinum-refractory advanced NSCLC, PD-L1 is associated with ambiguous outcomes as a predictive biomarker. Objective responses may occur in patients who are PD-L1 negative, and sometimes patients who tested positive for PD-L1 may not respond.[2-5,11] More optimal predictive and prognostic biomarkers are needed in everyday clinical practice.

The aim of the study was to investigate the real-world nivolumab and pembrolizumab efficacy in patients with platinum-refractory advanced NSCLC. We also sought the role of clinicopathologic prognostic and predictive factors.

PATIENTS AND METHODS

All consecutive patients aged over 18 years who were diagnosed as having platinum-refractory metastatic NSCLC and received at least one dose of nivolumab or pembrolizumab treatment at our centers between March 2017 and October 2021 were retrospectively reviewed from patient files, the center's databases, and chemotherapy ward files. The patients had disease recurrence or progression during or after at least one prior platinum-based doublet chemotherapy regimen. Ethical approval was obtained from the individual institutional ethical review committees and a consent waiver was granted in view of the retrospective nature of the evaluation. All procedures in the study that involved human participants were performed in accordance with the ethical standards of the institutional and/or national research committee, and also with the 1964 Declaration of Helsinki and its later amendments or comparable ethical standards.

Nivolumab was administered 3 mg/kg q14d, 240 mg q14d or 480 mg q28d and pembrolizumab was administered 200 mg q21d. Patient demographics; Eastern Cooperative Oncology Group Performance Status (ECOG PS) at the time of initiating nivolumab or pembrolizumab; smoking history; histology; molecular profiling for EGFR, ALK, ROS 1, and BRAF when available; PD-L1 status (Dako; Carpinteria, CA, USA) when available; sites of metastatic spread at the time of initiating nivolumab or pembrolizumab; post-progression treatments; number of nivolumab or pembrolizumab doses; response status, date of death or last follow-up; and immune-related adverse events (irAEs) were recorded.

The response assessment was performed mostly using computed tomography (CT) or fluorodeoxyglucose positron emission tomography (FDG PET)-CT every 3 months. Best radiographic response, i.e. complete remission (CR), progressive disease (PD), partial response (PR), and stable disease (SD), and the time to achieve the best response was recorded using the Response Evaluation Criteria In Solid Tumors (RECIST) criteria V 1.1 12. CR was defined as radiographic disappearance of all target lesions, PR was defined as a 30% decrease in target lesions, SD was defined as no significant increase or decrease in the size of the target lesions, and PD was defined as the appearance of the new lesions or an increase in the size of the known lesions (20% or more). The irAEs were determined, characterized, and graded by two investigators (O.D. and P.O.) according to the National Cancer Institute's Common Terminology Criteria for Adverse Events (CTACE), version 4.0.

Statistical Analysis

Demographic characteristics were described using frequencies and percentages for categorical variables and medians and ranges for continuous variables. OS was defined as the number of months between the first nivolumab or pembrolizumab treatment and death or censored at the date of the last patient follow-up. The objective response rate (ORR) was calculated as the percentage of patients achieving PR and CR among all treated patients. The disease control rate (DCR) was defined as the

percentage of patients achieving CR, PR, and SD. Progression-free survival (PFS) was defined as the number of months between the first pembrolizumab treatment and death or progression, whichever occurred first (censored at the date of the last patient contact). The duration of response (DoR) was defined as the time from the date of first response to the date of first documented disease progression, death, or last tumor assessment that could be evaluated.

The OS, PFS, and DoR curves were estimated using Kaplan–Meier analysis and compared using the log-rank test. Univariate and multivariate analyses were performed using a logistic regression model. A Cox proportional hazards model was used to identify independent predictive and prognostic factors. The multivariate models were fitted with the inclusion of the covariates that resulted as statistically significant in the univariate model. P< 0.05 was considered statistically significant in all analyses. Analyses were performed using the SPSS version 22 software (IBM Corp. Chicago, IL).

RESULTS

Patients

A total of 56 patients treated with nivolumab and pembrolizumab were retrospectively reviewed. The median duration of follow-up (defined as the time from initiation of ICI treatment to death or the date of the last follow-up visit) was 8.18 (range, 0.47 to 49.97) months. The baseline clinical and tumor characteristics at the initiation of ICIs are presented in Table 1. Of note, the median age was 66.5 (range, 35-88) years. The majority of patients were male (n= 50, 89.3%) and former or current smokers (n= 53, 94.6%). Just over half (51.8%) of the patients had an ECOG PS 0-1, 37.5% of patients were affected by squamous cell carcinoma and 12.5% had liver metastasis. There were two patients with driver mutations and seven patients had available PD-L1 results. Eight (14.3%) of patients had synchronous-metachronous cancer.

Table 1. Baseline patient and tumor characteristics

Age at start (years)	
Median	66.50
Range	35-88
Sex-no (%)	
Male	50 (89.3)
Female	6 (10.7)
Smoking status - no (%)	
Current or former smoker	53 (94.6)
Never smoked	3 (5.4)
Histology - no (%)	
Adenocarcinoma	31 (55.3)
Squamous cell carcinoma	21 (37.5)
Adenosquamous carcinoma	1 (1.8)
Large cell carcinoma	1 (1.8)
NSCLC, NOS	2 (3.6)
PD-L1 - no (%)	
Negative	4 (7.1)
1-49%	–
≤ 50%	3 (5.4)
Unknown	49 (87.5)
Driver mutations	
EGFR mutation	1 (1.8)
ALK translocation	1 (1.8)
Not assessed	21 (37.5)
EGFR-ALK wild type	33 (58.9)
ECOG performance status score - no (%)	
0-1	29 (51.8)
2-4	27 (48.2)
CNS metastasis - no (%)	
Yes	4 (7.1)
No	52 (92.9)
Liver metastasis - no (%)	
Yes	7 (12.5)
No	49 (87.5)
Bone metastasis - no (%)	
Yes	19 (33.9)
No	37 (66.1)
Malignant pleural effusion - no (%)	
Yes	10 (17.9)
No	46 (82.1)
Adrenal gland metastasis - no (%)	
Yes	14 (25.0)
No	42 (75.0)

Treatment

The majority of patients (n= 48, 85.7%) received ICIs as second-line therapy and nivolumab was the most commonly (n= 51, 91.1%) used ICI. Both patients with driver mutations received targeted therapy followed by platinum-based doublet chemotherapy. The median number of treatment cycles for nivolumab and pembrolizumab was 11 (range, 1 to 69) and 5 (range, 2 to 35), respectively. Twelve (21.4%) patients were still receiving nivolumab or pembrolizumab. Thirty-six (64.3%) patients discontinued treatment due to disease progression or

Table 2. Treatment characteristics of patients

Prior lines of therapy-no (%)	
1 prior line	48 (85.7)
2 prior lines	6 (10.7)
3 prior lines	2 (3.6)
Prior therapies-no (%)	
Platinum-based chemotherapy	56 (100.0)
Erlotinib[a]	1 (2.1)
Crizotinib[a]	1 (2.1)
Single agent chemotherapy[b]	6 (12.5)
Best response to most recent prior systemic regimen according to the investigator-no (%)	
Complete or partial response	23 (41.0)
Stable disease	8 (14.3)
Progressive disease	25 (44.7)
ICI choice-no (%)	
Nivolumab	51 (91.1)
Pembrolizumab	5 (8.9)
Reasons of discontinuation for ICIs-no (%)	44 (78.6)
Progressive disease or death	36 (64.3)
IRAEs	3 (5.4)
No evidence of disease and completed 2 years with ICI	5 (8.9)

[a]: patients who had driver mutations

[b]: patients who treated 2-3 prior lines of chemtherapy

death and 13 (23.2%) patients received subsequent systemic cancer therapy. The treatment characteristics are shown in Table 2.

Efficacy

Overall, 36 (64.3%) patients died by the time of the last follow-up (02/11/2021). The median PFS and OS were 7.06 (95%CI: 4.43-9.69) months (Figure 1) and 11.63 (95%CI: 7.65-15.61) months (Figure 2), respectively. In the entire study population, the ORR and DCR was 50.0% (CR: 16.1%, PR: 33.9%) and 60.7%, respectively. The median duration of responses was 26.40 months (95%CI: 4.17-48.76) (range, 0.67+ to 40.70+ months, with + indicating an ongoing response at the time of analysis). The patients who had CR discontinued treatment and all of them were disease-free at the time of analysis. The median duration of follow-up (defined as the time from the last cycle of ICI treatment to date of the last follow-up visit) for disease-free patients was 12.4 months (range, 4.0+ to 24.3+ months).

Prognostic and Predictive Factors

We evaluated the prognostic and predictive role of ECOG PS, histologic subtype, age at initiation of ICIs, number of prior therapies, site of metastatic location, and irAEs (Table 3). Bone metastasis and liver metastasis were associated with worse PFS and irAEs were associated with better PFS in the univariate analysis. In the final multivariate model, irAEs remained independently associated with superior PFS. As shown using representative Kaplan-Meier survival curves (Figure 3), patients with irAEs had significantly longer median PFS outcomes (log-rank p= 0.004).

The univariate analysis revealed that number of prior therapies and irAEs were associated with OS. In the multivariate analysis, irAEs were independently associated with better OS. The median overall survival was not estimated in patients with irAEs and 10.50 months in those without irAEs (log-rank p= 0.008) (Figure 4).

Logistic regression analysis revealed that ECOG PS was associated with lower DCR. Table 4 summarizes the univariate and multivariate analyses of ORR and DCR.

DISCUSSION

In our study cohort, patients with previously treated advanced NSCLC, OS outcomes compatible with randomized studies, whereas PFS, ORR and DCR results were better. There were no patients with driver mutations other than two patients with EGFR mutations and ALK rearrangements in our study, whereas RCTs included 10-19% of patients with driver mutations. ICIs are associated with poor PFS, OS, and lower likelihood response rates in patients with NSCLC with a driver mutation.[2,4,5,13-15] ICIs were shown to have worse efficacy in never-smoked patients than in current or former smokers in terms of PFS and OS.[16-19] Smoking history is significantly associated with tumor mu-

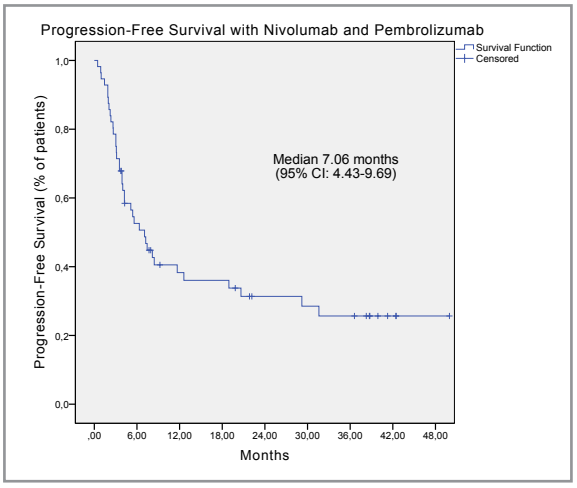

Figure 1. Kaplan-Meier curve of progression-free survival (PFS) in the global population (95%CI, 95% confidence interval)

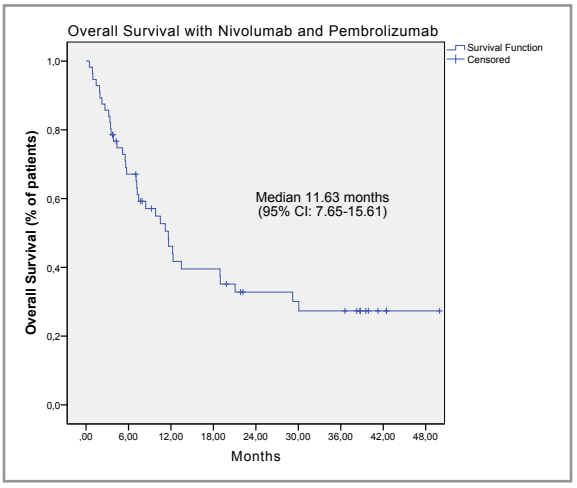

Figure 2. Kaplan-Meier curve of overall survival (OS) in the global population (95%CI, 95% confidence interval)

tation burden.[20,21] Higher tumor mutational burden tends to have more immunogenic neoantigens and is associated with a higher likelihood of response to ICIs.[20,22-25] In RCTs, 7-20% of patients were never-smoked; only three patients were never-smoked in our study cohort.[2-5] ICIs are associated with less benefit in patients with advanced NSCLC with CNS metastasis and constitute 7-15% of patients in RCTs.[2-5,11,26,27] In our study cohort, only four patients had CNS metastasis. Liver metastasis is a well-known poor prognostic factor, also in patients with advanced NSCLC. In our study cohort, 12.5% of patients had liver metastasis, which was less than in RCTs.[28-31] Therefore, we expected better outcomes in our study cohort than in randomized studies. Clinical responses were evaluated

Table 3. Univariable and multivariable analyses of progression-free survival (PFS) and overall survival (OS)

	Progression-free survival (PFS)				Overall survival (OS)			
Variables	**Unadjusted HR (95%CI)**	**p**	**Adjusted HR (95%CI)**	**p**	**Unadjusted HR (95%CI)**	**p**	**Adjusted HR (95%CI)**	**p**
ECOG PS ≥ 2	1.19 (0.62-2.27)	(0.585)	-		1.24 (0.64-2.40)	0.519	-	
Histology-Non-SQ	1.37 (0.70-2.69)	0.350)	-		1.53 (0.76-3.06)	0.229	-	
Age at start ≥ 65 years	0.75 (0.39-1.44)	0.394	-		0.87 (0.45-1.70)	0.699	-	
Number of prior therapies ≥ 2 vs. 1	0.34 (0.10-1.13)	0.080	-		0.22 (0.05-0.92)	0.039	0.30 (0.07-1.31)	0.111
Presence of brain metastasis	2.20 (0.77-6.26)	0.138	-		1.72 (0.52-5.64)	0.371	-	
Presence of bone metastasis	1.94 (1.01-3.72)	0.045	1.43 (0.68-2.97)	0.336	1.68 (0.86-3.27)	0.123	-	
Presence of adrenal gland metastasis	0.68 (0.31-1.50)	0.350	-		0.66 (0.28-1.51)	0.331	-	
Presence of malignant pleural effusion	1.03 (0.43-2.48)	0.941	-		1.09 (0.45-2.62)	0.845	-	
Presence of liver metastasis	2.49 (1.09-5.71)	0.030	1.56 (0.62-3.95)	0.343	2.26 (0.93-5.51)	0.072	-	
irAEs	0.17 (0.04-0.74)	0.018	0.17 (0.04-0.74)	0.020	0.17 (0.04-0.74)	0.018	0.22 (0.05-0.95)	0.044

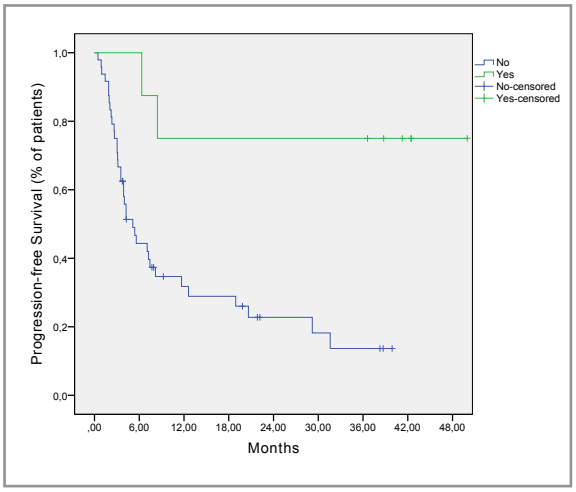

Figure 3. Kaplan-Meier plot for the progression-free survival (PFS) stratified by immune-related adverse events (IRAEs) (95%CI, 95% confidence interval) (NE: Not estimated)

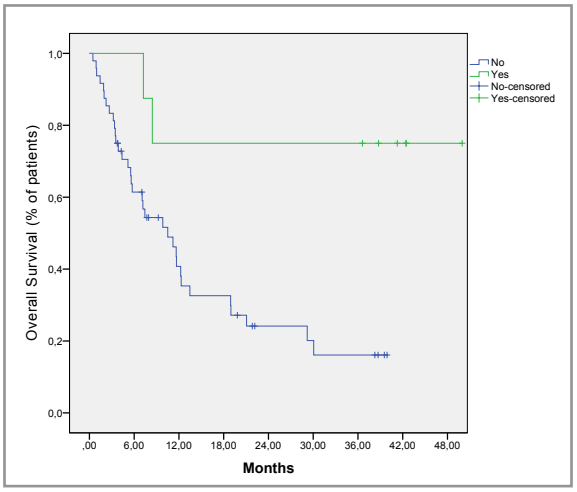

Figure 4. Kaplan-Meier plot for the overall survival (OS) stratified by immune-related adverse events (IRAEs) (95%CI, 95% confidence interval) (NE: Not estimated)

by the investigators of this study according to local radiology and nuclear medicine reports instead of independent radiology reviewers. This might cause some bias such as misclassification of the responses as PR instead of SD. The retrospective design and relatively low patient number may affect the results. Therefore, PFS and ORR results could be overestimated in our study cohort. However, 16.1% of patients had CR with ICIs in our study cohort and all were disease-free at the time of analysis, which is far better than in RCTs.[2-5,32]

Several real-life experience studies showed worse outcomes than in the experimental arms of RCTs.[33-35] Clinical trials are an essential tool of premarket evaluation of a medical product. Eligibility criteria for RCTs should be sufficiently strict to control bias and achieve internal validity. However, strict eligibility criteria cause restriction on the diversity of patients and raise concerns about generalizability.[9,36] RCTs included only patients who had ECOG PS 0-1. In several real-life experience studies, poor PS was associated with inferior survival outcomes.[33,34,37,38] In our study cohort, 48.2% of patients had ECOG PS 2-4 and this was independently associated with lower DCR. However, we found no association between poor ECOG PS and survival outcomes. The statistical difference that

Table 4. Logistic regression analysis of the objective response and disease control

Variables	Objective response Unadjusted OR (95%CI)	p	Disease control Unadjusted OR (95%CI)	p	Adjusted OR (95%CI)	p
ECOG PS ≥2	0.48 (0.16-1.40)	0.184	0.25 (0.08-0.79)	0.019	0.24 (0.07-0.81)	0.021
Histology-Non-SQ	0.63 (0.21-1.87)	0.409	0.47 (0.14-1.51)	0.207	-	
Age at start (years) ≥ 65 years	1.35 (0.46-3.95),	0.585	1.52 (0.51-4.56)	0.448	-	
Number of prior therapies ≥ 2 vs. 1	2.82 (0.49-15.99),	0.240	1.72 (0.41-13.70)	0.539	-	
Presence of bone metastasis	0.61 (0.20-1.88)	0.399	0.30 (0.09-0.97)	0.045	0.29 (0.08-1.00)	0.051
Presence of brain metastatsis	0.30 (0.03-3.16)	0.322	0.19 (0.01-1.97)	0.165	-	
Presence of adrenal gland metastasis	2.17 (0.62-7.61)	0.222	1.87 (0.50-6.95)	0.347	-	
Presence of malignant pleural effusion	0.61 (0.15-2.45)	0.488	0.58 (0.14-2.32)	0.447	-	
Presence of liver metastasis	0.35 (0.06-2.00)	0.240	0.21 (0.03-1.21)	0.081	-	
irAEs	3.54 (0.64-19.37)	0.144	5.44 (0.62-47.75)	0.126	-	

might have occurred between ECOG PS 0-1 vs. ECOG PS 2-4, probably dampened due to better than expected response rates and survival results.

Various studies investigated predictive/prognostic biomarkers and clinicopathologic factors for ICI efficacy. For patients with platinum-pretreated advanced NSCLC, there is no reliable biomarker. Several studies showed that irAEs were associated with durable response to ICIs and superior clinical outcomes. Although the precise mechanism of association remains unclear, irAEs are probably due to activated T cells and shared tumor antigens in host tissues.[39-41] In our study cohort, patients who developed irAEs were associated with better PFS and OS, which was consistent with the literature. The therapy line with ICIs affected the outcomes in advanced with patients NSCLC, and third or later-line therapies were significantly associated with inferior OS and PFS.[42] We stratified patients as one prior-line vs. two or more therapies and there was no association with therapy line in our study cohort. In fact, there was a trend to statistical significance between better OS and two or more prior treatments. We need more studies to confirm this finding and reveal the underlying mechanism.

We sought a predictive and prognostic role of common sites of metastasis. Tumor microenvironments differ across various organ sites and they may affect the activity of ICIs.[43,44] Liver metastasis is a well-known poor prognostic site of metastasis.[28,29] However, multivariate analysis revealed no statistically significant association for patients with liver metastasis in terms of PFS and OS in our study cohort probably due to low patient numbers with liver metastasis. Bone and bone marrow are immune regulatory organs.[45,46] Therefore, ICI responses may be affected by bone metastasis. Patients with bone metastasis had a trend to statistical significance for poorer PFS and DCR in our study cohort. None of the randomized studies with ICIs specifically stratified patients according to the presence of bone metastasis. In a nivolumab expanded-access program, bone metastasis was associated with a lower likelihood of response, and poorer PFS and OS.[47] In another retrospective study, organ-specific responses with nivolumab in patients with advanced NSCLC were investigated. Nine of 12 patients with bone metastases had progressive disease.[43] Our study results were compatible with these studies.

Our study has several limitations. The retrospective design and relatively small sample size limited the significance of the subgroup analysis. PD-L1 analyses were not available in most of the patients. In conclusion, this bi-centric real-world data demonstrated that ICIs are standard of care in patients with platinum-refractory advanced NSCLC, even in those who had poor ECOG PS and received multiple-line therapy.

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